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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,825	03/22/2001	Keith D. Allen	R-849	6413

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DELTAGEN, INC.
ATTN: JOHN E. BURKE
1003 HAMILTON AVENUE
MENLO PARK, CA 94025

EXAMINER	
PAPPU, SITA S	

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 03/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,825	ALLEN ET AL.	
	Examiner	Art Unit	
	Sita pappu	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *16,41 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-40 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Currently, claims 1-48 are pending in the instant application. This Office Action is in response to a communication filed by the Applicant in paper # 10, on 02/06/2002.

Election/Restrictions

Applicants' election, with traverse, of Invention III, claims 8-11, 12, 17-26, 28-36, and 42-47, in paper #10, filed 02/06/2002, is acknowledged. Applicants argued that the restriction requirement is not proper and the argument is based on the grounds that the Inventions are all related and that examination of the other Inventions would not seriously burden the examiner. Applicant's arguments are taken into consideration and Group I, claims 1-4, drawn to a targeting construct, Group II, claims 5-7, drawn to embryonic stem cell, Group IV, 13-15, 27, 37-40, drawn to a method of identifying an agent that modulates the expression of cGMP phosphodiesterase gene using a transgenic animal, are, hereby, rejoined with the elected Invention of Group III, claims 8-11, 12, 17-26, 28-36, and 42-47, and are being examined together, on their merits. Groups V and VI, claims 16, 41, and 48, drawn to an agent, are not rejoined with Group III. This restriction requirement is made FINAL.

Claims 16, 41 and 48 are withdrawn from consideration as drawn to non-elected subject matter. This paper contains an examination of the claims 1-15, 17-40, 42-47 on their merits.

Drawings

Drawings are objected to by the draftsperson. See attached PTO-948.

Claim Rej ctions - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 17-40, 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene, does not reasonably provide enablement for any transgenic animal and any knockout animal containing an altered allele for the cGMP phosphodiesterase gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 1-15, 17-40, 42-47 are drawn to a non-human transgenic animal comprising a disruption in cGMP phosphodiesterase gene, a cell from that transgenic animal, and a method of identifying an agent that modulates the expression of a cGMP phosphodiesterase gene, the method comprising: administering an agent to the non-human transgenic animal and determining whether the expression of cGMP phosphodiesterase in the non-human transgenic animal is modulated wherein the modulation is effected in the form of phenotypic changes that include eye abnormalities and hyperactive behavior. Thus, the nature of the invention is directed to transgenic animal and methods of using the transgenic animals in identifying agents that modulate gene expression.

Breadth of Claims:

In the instant case, the claims 1-15, 17-40, 42-47 are drawn to a transgenic animal which is also a knockout animal containing an altered allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase. Claims 1-15, 17-40, 42-47 encompass any transgenic animal containing a disrupted allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase. The specification does not provide an enabling disclosure for such a transgenic animal. The only embodiment enabled by the specification within the scope of claims 1-15, 17-40, 42-47 is for a knockout mouse containing an altered allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the altered allele is a nonfunctional cGMP phosphodiesterase allele. Thus the breadth of claims is very broad and encompasses any transgenic animal with a disruption in the gene

encoding a cGMP phosphodiesterase and includes any and all mutant forms, substitutions, deletions, or insertions in the gene.

The specification only teaches how to use a homozygous, knockout mouse containing two disrupted alleles for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the gene knocked out corresponds to the gene that encodes the cGMP phosphodiesterase in question. The specification does not teach how to make and use the invention with any and all transgenic animals and with any knockout animal with any form of disruption in the gene encoding cGMP phosphodiesterase, as claimed in the claims 1-15, 17-40, 42-47. The breadth and scope of claims 1-15, 17-40, 42-47, thus surpass that enabled by the specification.

Amount of guidance in the specification and Working Examples:

The specification discloses the use of a specific cGMP phosphodiesterase gene as identified by SeqID NO:19 or by the GenBank accession number X60664 (page 7, line 12; page 59, line 30) in producing the transgenic, knockout mouse of the instant invention and use the KO mouse to screen for agonists and antagonists of cGMP phosphodiesterase (page 39, line 15) that modulate its expression and/or function through the use of known screening methods wherein the modulation is effected in the form of phenotypic changes that include eye abnormalities and hyperactive behavior. The working examples (page 60, line 8) demonstrate that only homozygous mice exhibited the phenotypes that are claimed and include various eye abnormalities and hyperactive behavior while the heterozygous mice exhibited only a discoloration of the eye (page 61, line 8).

The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the gene knocked out is a nonfunctional cGMP phosphodiesterase gene. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and they do not provide enough guidance on how to practice the invention with any transgenic mouse carrying any and all transgene(s) of the types recited in the claims. Further, the specification and the working examples do not provide enough guidance on how to practice the invention with any and all knockout mice, including a heterozygous mouse of the instant invention which does not exhibit the claimed phenotypes of eye abnormality, as claimed in claims 17-23, 28-32, 35, 36, 39, 40, and of hyperactive behavior as claimed in claims 42-47. In particular, the eye discoloration and pink eye exhibited by the heterozygous mice is an unpredicatable indicator of the modulation by the agent used because eye discoloration and pink eye can be a result of any number of things other than a modulation by the test agent used such as dust or other allergens.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as

claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the gene knocked out is a nonfunctional cGMP phosphodiesterase gene. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous cGMP phosphodiesterase knockout mouse. The claims encompass heterozygotes, but since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. Thus, the phenotype of a transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. Further, in the instant case, In particular, the eye discoloration and pink eye exhibited by the heterozygous mice is an unpredicatable indicator of the modulation by the agent used because eye discoloration and pink eye

can be a result of any number of things other than a modulation by the test agent used such as dust or other allergens. Thus, the specification is enabling for a method of identifying an agent that modulates the phenotype of a KO mouse using only a homozygous KO mouse of the instant invention.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the invention while being enabled for a homozygous knockout mouse containing two disrupted alleles for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase gene, does not extend the predictability of the invention to other animal systems.

Further, the particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with the breadth of the scope as claimed in claims 8, 9, 11, 12, 15 is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of transgenic animals besides mice having a disruption in the cGMP phosphodiesterase gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are

offered in regard to how one would have prepared any other type of animal. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1. Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice of the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be

required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed in claims 8, 9, 11, 12, 15. Thus, the enabled scope of the claims is limited to a homozygous knockout mouse containing two disrupted alleles for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the gene knocked out is a nonfunctional cGMP phosphodiesterase gene and exhibits a specific phenotype as described.

Claims 8, 11, 12, 15, 17-40, 42-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, No. 4, pp. 1099-1111 (also available at www.uspto.gov).

Claims 8, 11, 12, 15 are directed to a transgenic and/or knockout animal containing an altered allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase. However, the specification only describes a single species of a transgenic, knockout mouse of the type claimed. In analyzing whether a written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, claims 8, 11, 12, 15 encompass the whole genus of 'transgenic animals' and include any and all transgenic animals that contain an altered allele for the

gene that naturally encodes and expresses a functional cGMP phosphodiesterase. However, the specification describes only a single species of homozygous, knockout mouse of the type containing two disrupted alleles for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the gene knocked out is a nonfunctional cGMP phosphodiesterase gene and exhibits a specific phenotype as described in claims 17-23 and 42. Thus for the claims to meet the written description requirement, other representative species of transgenic animals containing an altered allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the gene knocked out is a nonfunctional cGMP phosphodiesterase gene and exhibits a specific phenotype as described in claims 17-23 and 42, should be described by their complete structure or by other relevant identifying characteristics, in the specification.

Next, then, it is determined if a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant case, no identifying characteristics are provided for the claimed genus of transgenic animals. Thus the limited information in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed genus of 'transgenic animals'. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus of 'transgenic animals'.

Similarly, claims 17-40 encompass any KO animal exhibiting the phenotype (s) described in the claim(s) while the specification describes only a specific knockout

mouse containing an altered allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase gene wherein the gene knocked out corresponds to the gene that encodes the cGMP phosphodiesterase gene in question and exhibits a specific phenotype as described in claims 17-23 and 42.

Similarly, claims 42-47 encompass any KO animal exhibiting the phenotype (s) described in the claim(s) while the specification describes only a specific knockout mouse containing a specific altered allele for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase gene wherein the gene knocked out corresponds to the gene that encodes the cGMP phosphodiesterase gene in question and exhibits a specific phenotype as described in claims 17-23 and 42.

Thus, for claims 8, 11, 12, 15, 17-40, 42-47 to satisfy the written description requirement, and to establish that the applicants had the invention in their possession at the time of the application, the claims in question should clearly recite the invention which, in the instant application, is a homozygous KO mouse containing two disrupted alleles for the gene that naturally encodes and expresses a functional cGMP phosphodiesterase wherein the gene knocked out is a nonfunctional cGMP phosphodiesterase gene and exhibits a specific phenotype as described in claims 17-23 and 42.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Claim 1 is drawn to a targeting construct comprising steps (a) through (d), wherein step (b) is missing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 17-40, 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baehr et al. (1991; FEBS letters vol. 278, no. 1, pp107-114) Lem et al. (1992; Proc. Natl. Acad. Sci., USA, vol. 89, no.10, pp4422-4427), and further in view of Tanabe et al. (1998; IOVS, vol. 39, no.4, pp S1118).

Baehr et al. teach the nucleotide sequence of the alpha subunit of murine cGMP phosphodiesterase gene (Fig. 2, page 108) involved in hydrolyzing cGMP (page 107, left column, lines 3-6).

Baehr et al. do not teach the use of their polynucleotide sequence to generate KO mice.

Lem et al. teach that retinal degeneration is rescued in transgenic mice by expression of the cGMP phosphodiesterase beta subunit and thus, teach the involvement of cGMP PDEs in retinal abnormalities and that they can be rescued by cGMP PDEs (page 4422, right column, line 4).

Lem et al. do not teach their method with cGMP PDE alpha subunit.

Tanabe et al. teach PDE gamma KO mice and thereby demonstrate that generation of KO mice is a successful way of studying cGMP function and expression (see conference abstract, 5153).

Tanabe et al. do not teach their KO mice with cGMP PDE alpha subunit.

Therefore it would have been obvious to one of ordinary skill in the art to use the nucleotide sequence of Baehr et al. to generate knockout mice and use them as model systems to screen for agents that modulate the function and/or expression of alpha subunit of cGMP phosphodiesterase, with a reasonable expectation of success. The motivation to do so was provided by Tanabe et al. who successfully demonstrated that KO mice can be used as model systems to study PDE function, and the methods of making KO mice and methods of screening for compounds using the KO mice are well known in the art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746 7442 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-2982.

S. Pappu
March 4, 2002

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600